37. A method according to claim 19, wherein the carrier comprises a biopolymer, for example collagen or hyaluronic acid or a polymer of PVC, for contacting or implanting into the wound/fibrotic lesion so as to allow release of the active agents slowly or quickly and to provide *in situ* activity.--

REMARKS

Claims 1 and 3-37 are now pending in the application. New claims 23-27 have been added herein. Claims 1, 17, 19 and 21 have been amended herein to more particularly point out and distinctly claim the invention. Support for these amendments may be found in the original claims as filed, and, for claim 19, in the description of the method in the specification at page 5, lines 4-24 (not counting blank lines). The new claims, dependent on method claim 19, are method claims which correspond to the claims dependent on claim 1, and are therefore supported in the claims as originally filed.

Applicants' Invention

Applicants' invention relates to compositions comprising non-fibrotic growth factors and fragments, such as TGFβ-3 or FGF or their fragments, to promote wound healing with little or no scarring as compared to natural healing processes. The TGFβ-3 non-fibrotic growth factor or fragments are used in combination with (1) fibrotic growth factors, such as TGFβ-1, TGFβ-2, PDGF, and mixtures of two or more thereof, wherein the fibrotic growth factors are present in a lower proportion than the non-fibrotic growth factor compared to the growth factors present naturally in wounds or disorders in question, or (2) with such

fibrotic growth factors together with anti-fibrotic agents against them. These agents are incorporated into a pharmaceutically acceptable carrier, in an amount effect to result in healing of wounds with reduced scarring compared to natural healing processes and for treatment of fibrotic disorders. Applicants have discovered a novel means to promote healing by using TGFβ-3 or fragments to overcome scarring which would normally occur.

At page 8 through page 15 of the specification, Applicants have included experimental data showing tests individually using TGFβ-1, TGFβ-2 or TGFβ-3. Additionally, tests were run where antibodies for neutralizing TGFβ-1 (anti-TGFβ-1) and TGFβ-2 (anti-TGFβ-2) were used. Wounds treated with TGFβ-3, anti-TGFβ-1 and anti-TGFβ-2 have less fibronectin and better orientation, than wounds treated with TGFβ-1 or TGFβ-2, which have increased fibronectin with abnormal orientation. Additionally, wounds treated with TGFβ-3 contained a low profile of macrophages, while wounds treated with TGFβ-1 and TGFβ-2 contained a higher profile of macrophages. TGFβ-3 treated wounds develop more blood vessels compared to the control wounds or wounds treated with TGFβ-1 or TGFβ-2. Applicants note that this is a marked effect. Wounds treated with TGFβ-3, anti-TGFβ-1 and anti-TGFβ-2 have collagen having a similar reticular pattern to the surrounding dermis, while wounds treated with TGFβ-1 and TGFβ-2 and the control wounds have abnormal orientation of collagen.

As the data shows, TGFβ-3, unlike TGFβ-1 or TGFβ-2, acts to reduce wound scarring. Additionally, using anti- TGFβ-1 and anti-TGFβ-2 improves wound healing by reducing scarring.

Rejections under 35 U.S.C. §§102(b) and 103(a)

Applicants gratefully acknowledge withdrawal of the rejection under 35 U.S.C. §102(b) over Geistlich et al.

Claims 1 and 4-22 stand rejected under 35 U.S.C. §102(b) over Ammann et al., on the ground that Ammann et al. teach compositions comprising TGFβ-3, and that the present claim drawn to TGFβ-3 alone reads on Ammann et al.

Claims 1, 2, 6, 7, 12 and 14-20 stand rejected under 35 U.S.C. §102(b) as anticipated by Cerletti. The rejection states that Cerletti teaches a method for treating wounds with TGFβ-like proteins and that Cerletti teaches TGFβ-1, TGFβ-2 and TGFβ-3.

Claims 1 and 3 stand rejected under 35 U.S.C. §103 over Cerletti et al. or Ammann et al. in view of Baird, et al., on the above ground with respect to Cerletti and Ammann, and that Baird et al. discloses FGF, and that FGF may be used for wound healing. The Examiner stated that combination of two compositions each of which is taught by the prior art to be useful for the same purpose is not patentable.

Claims 1 and 21 have been amended herein. As presently amended, Applicants' claims are directed to a composition, comprising TGFβ-3, either (1) with fibrotic growth factors or fragments thereof present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question, or (2) with such fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or PDGF, all in a pharmaceutically acceptable carrier in an amount effective for healing of wounds with no or at least reduced scarring and for the treatment of fibrotic disorders. The claims as presently amended are believed to distinguish over each of the cited references

and combinations thereof. Because neither Cerletti et al. nor Ammann et al., nor either of these references taken in view of Baird et al., teach or suggest a composition comprising TGFβ-3 with fibrotic growth factors or fragments thereof present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question, or with such fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or PDGF, all in a pharmaceutically acceptable carrier, the present claims are believed to be in allowable condition. Accordingly, Applicants request withdrawal of the rejections over Ammann, et al., Cerletti et al. and over either of Ammann et al. or Cerletti et al. in view of Baird et al. Notice to such effect is respectfully solicited.

Amended claim 19 distinguishes over the cited references for the same reasons as set forth above with respect to the composition claims. The method claim is distinguished from the Cerletti reference in particular since Cerletti uses amounts of TGFβ-3 which would not give the reduced scarring effect achieved by the present invention. Cerletti teaches TGFβ-3 and the other TGFβ's as fibrotic growth factors and does not teach or suggest that TGFβ-3 may be used, as presently claimed, in order to promote healing with reduced scarring and for the treatment of fibrotic diseases.

35 U.S.C. §112 Rejections

Applicants acknowledge with gratitude withdrawal of the rejection of claim 4 regarding the anti-fibrotic agents, and rejection of claims 1, 4 and 5 regarding how the claimed agents are to be directed into the cell nucleus, under 35 U.S.C. §112, first paragraph.

The specification is objected to and claims 1, 4 and 5 stand rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure. Specifically, it is alleged that Applicants have failed to provide the concentration of agents. The Examiner asserts that, assuming equimolar amounts of such agents are intended that such equimolar amounts will expectedly bind each other and thereby be rendered useless in such a composition for use in treating wounds.

A person of ordinary skill in the art at the time the invention was made would have known how to use such a composition, and would recognize how to set the concentrations of the agents to achieve the desired end. First, Applicants incorporate by reference and reiterate the arguments set forth in the previous reply to Office Action in response to this ground of rejection.

Second, Applicants point out that with respect to use of TGFβ-3 with fibrotic growth factors or fragments thereof, the claims specifically state that the fibrotic growth factors or fragments thereof are present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question. Use of an effective amount of a pharmaceutical ingredient is acceptable to provide the guidance required by section 112 when the specification provides such information. The phrase "an effective amount . . . for growth stimulation" was held to be definite where the amount was not critical and those skilled in the art would be able to determine from the written disclosure, including the examples, what an effective amount is. In re Halleck, 422 F.2d 911, 164 USPQ 647 (CCPA 1970); MPEP §2173.05(c). In the specification at page 8, the experimental section cites Shah et al, The Lancet, 339, 213-214, 1992 as the source for the experimental protocol.

A copy of this reference has been obtained and is included with this response. As is apparent therefrom, the amounts to be administered are adequately set forth therein. Thus, with respect to use of TGFβ-3 with fibrotic growth factors or fragments thereof, Applicants respectfully submit that this rejection should be withdrawn.

Third, with respect to the use of TGFβ-3 with fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or PDGF, Applicants submit that the specification adequately discloses to a person of ordinary skill in the art how to use the composition. In the specification at page 2, lines 16-17, two references are cited which provide guidance for use of this embodiment. Specifically, these references are (1) Shah, et al., The Lancet, 338, 213-214, 1992 (copy enclosed); and (2) WO 91/04748. As is set forth in these references, a person of ordinary skill in the art would know how to set or determine the proper relative concentrations of the claimed components.

With respect to the various agents binding with each other, these agents will not bind with each other and render each other useless because, the antibodies are not rendered useless by reacting with and neutralizing an antigen on a one-to-one basis. To the contrary, a given antibody is able to react with and neutralize multiple antigens. Thus, even if equimolar amounts of antigen and antibody were present, the antibodies would not be bound up and rendered useless by the antigens. Furthermore, the purpose of the antibodies is to reduce the amount of TGFβ-1, TGFβ-2 or PDGF with respect to the naturally occurring amount of TGFβ-3 present in the composition. In other words, if a source of TGFβ provided these growth factors in a natural ratio, scarring would occur

during the healing, and this TGFβ would not be useful for treating fibrotic disorders. By adding antibodies to TGFβ-1, TGFβ-2 or PDGF, the amounts of these are reduced relative to the amount of TGFβ-3, providing a composition which is useful for reducing scarring and treating fibrotic disorders, as claimed. Thus, there is no contradiction in providing a composition which includes both antigens and antibodies thereto.

Finally, Applicants note that in setting forth this ground of rejection, the Examiner stated:

> The claims are directed to a composition comprising an non-fibrotic growth factor [e.g., TGFβ-1] together with an anti-fibrotic agent [e.g., an antibody to TGFβ-1].

This statement is in error, since *TGFβ-1 is a **fibrotic** growth factor.* Applicants' foregoing remarks are premised on the basis that the Examiner intended to use the term "fibrotic" rather than "non-fibrotic" in the above-quoted sentence. As has been set forth throughout this reply and the in specification, TGFβ-3 is a non-fibrotic growth factor, whereas TGFβ-1, TGFβ-2 and PDGF are fibrotic growth factors. If Applicants' understanding of this rejection is incorrect, the Examiner is respectfully requested to correct and clarify the basis therefor.

For the reasons set forth above, Applicants request withdrawal of the rejection of claims 1, 4 and 5 under 35 U.S.C. §112, first paragraph, on this ground.

In view of the amendments to the claims and the above comments, Applicants submit that the claims are now in condition for allowance. In the event any issues remain in the prosecution of this application, Applicants request that the Examiner call the undersigned attorney to expedite allowance of the claims. If any fees are required for the

filing of these papers, Applicants request the Commissioner to charge those fees to deposit account #18-0988.

Respectfully submitted,

RENNER, OTTO, BOISSELLE & SKLAR, P.L.L.

By _____
Thomas W. Adams
Reg. No. 35,047

1621 Euclid Avenue
Nineteenth Floor
Cleveland, Ohio 44115
(216) 621-1113

G:\SHARED\ADAMS\mcne\MCNE109.AM4.wpd